Prognostic stratification in venetoclax-based acute myeloid leukemia treatments: the molecular prognostic risk signature tested in a real-world setting

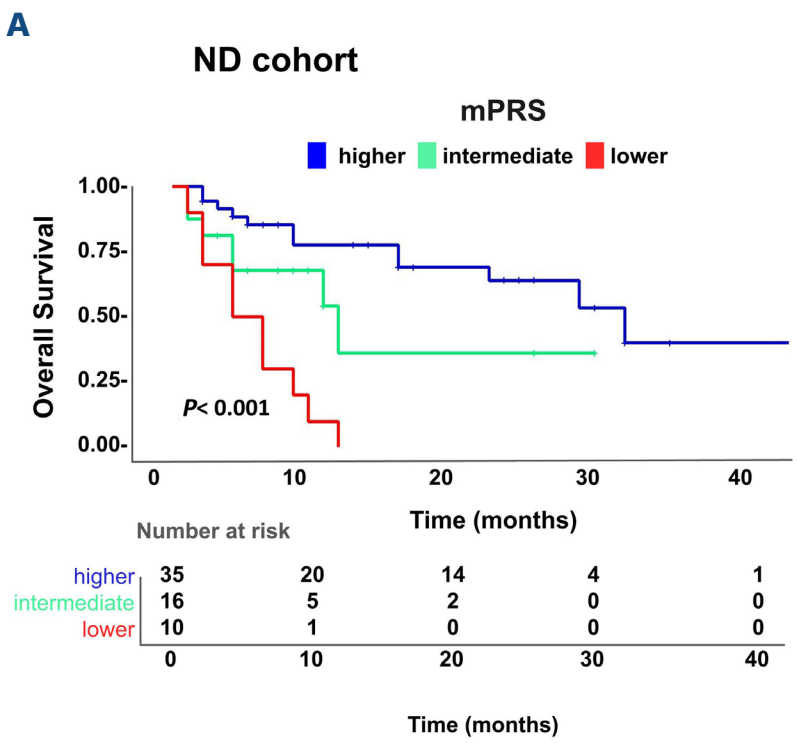
Genotype-based stratification models used in acute myeloid leukemia (AML), such as the European LeukemiaNet (ELN) 2022 risk classification,[1] have been developed based on patients treated in a conventional intensive chemotherapy setting and their performance in outcome prediction for patients treated with venetoclax-based combinations is unsatisfactory. Bataller *et al.*[2] recently reported a single-center, retrospective study in patients with newly diagnosed (ND) AML treated with venetoclax and hypomethylating agents - either included in, or outside, a clinical trial - aiming to validate the molecular prognostic risk signature (mPRS) developed by Döhner *et al.* using mutational data from the phase Ib trial (NCT02203773) and the pivotal phase III VIALE-A trial.[3] In the particular study patients were allocated, according to the mutational status of four genes, to a lower benefit (*TP53*^{mut}), an intermediate benefit (*FLT3*-ITD^{mut} or *N/KRAS*^{mut}) or a higher benefit (none of the above) group.[3] The construction of this model stemmed from evidence that refractoriness and adaptive resistance to venetoclax are largely attributable to the presence and/or emergence of clones harboring the aforementioned mutations.[4] In the study by Bataller *et al.*, mPRS effectively stratified treatment-naïve AML patients into the three risk groups with statistically significant differences in median overall survival (OS) and event-free survival (EFS).[2] A different stratification model for relapsed/refractory (R/R) AML patients treated with venetoclax-based combinations, proposed by Krüger *et al.*,[5] stratifies patients into three risk groups based on the mutation profile of eight genes, resulting in favorable (*STAG2*^{mut}, *BCOR*^{mut} or *SF3B1*^{mut}), adverse (*TP53*^{mut}, any *FLT-3*^{mut}, *CBL*^{mut}, *PTPN11*^{mut} or *NF1*^{mut}) and intermediate (none of the above) risk categories.

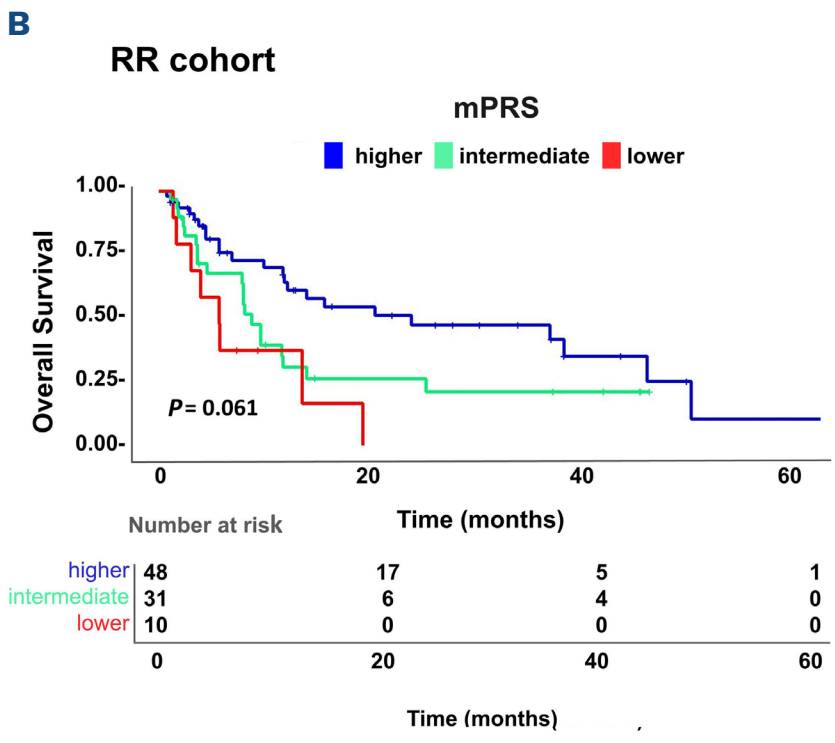
We set out to assess the reproducibility of those observations in ND AML patients and also to extend the analysis to R/R patients in our institutional, real-world cohort of patients receiving venetoclax-based combinations from January 2015 to December 2023. The study was approved by the local institutional review board. Written informed consent was obtained in accordance with the Declaration of Helsinki. The performance of different stratification models was assessed and compared using Harrell's concordance index (C-index). We identified 89 R/R and 61 ND patients; their clinical characteristics are summarized in *Online Supplementary Table S1*. The partner drug was azacitidine in 129 (86%), decitabine in eight (6%) and low-dose cytarabine in 12 (8%) patients.

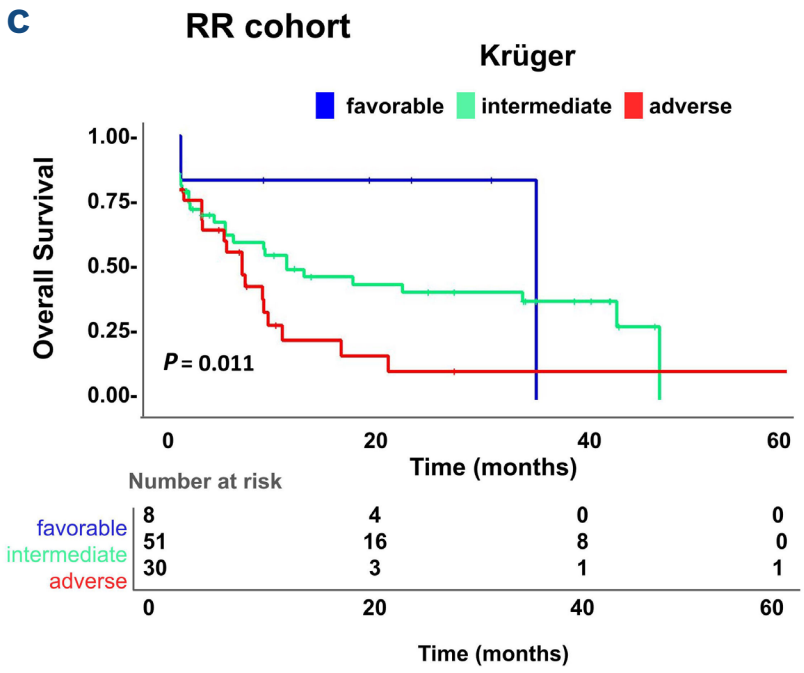
According to the mPRS stratification model in the ND cohort, 35 (57%), 16 (26%) and 10 (17%) patients were allocated to the higher-, intermediate- and lower-benefit group, respectively. The overall response rate, which included patients experiencing complete remission (CR) and CR with incomplete hematological recovery (CRi), was 77%, 19% and 40% (P<0.001), respectively. When using the ELN 2022 risk stratification model, the overall response rate was 54%, 37% and 57% in the favorable, intermediate and adverse categories, and the difference was not statistically significant (P=0.593). Among patients in CR or CRi with available minimal residual disease data, 11/24 (46%) in the higher-, 0/2 (0%) in the intermediate- and 0/3 (0%) in the lower-benefit mPRS groups were negative for minimal residual disease (P=0.157).

We then compared the predictive power of the mPRS model and the ELN 2022 classification system for OS and EFS. The median OS was 30, 11 and 4 months in the higher-, intermediate- and lower-benefit groups according to the mPRS model (P<0.001; C-index=0.69) (Figure 1A, D) and not reached, 27 and 11 months for the favorable, intermediate and adverse ELN 2022 categories, respectively (P=0.177; C-index=0.590). The median EFS was 13, 1 and 2 months for the mPRS groups (P<0.001; C-index=0.70) (Figure 2A, D) and 25, 1 and 6 months for the ELN 2022 categories (P=0.088; C-index=0.49). The mPRS *versus* ELN 2022 classification system Z-score was 2.22 (P=0.030) (Figure 1D) for OS and 4.4 for EFS (P<0.001) (Figure 2D). In keeping with the observations by Döhner *et al.*[3] and Bataller *et al.*,[2] mPRS outperformed the ELN 2022 classification system in ND AML patients.

We then set our focus on R/R patients receiving venetoclax-based lower intensity salvage treatments and repeated the above analyses in this setting. Forty-eight (54%), 31 (35%) and ten (11%) of the patients were stratified into the higher-, intermediate- and lower-benefit groups, respectively. The overall response rate was 73%, 48% and 20% in the three groups (P=0.003) and 80%, 52% and 58% in the favorable, intermediate and adverse ELN 2022 risk categories (P=0.147). In the relapsed subcohort, the overall response rate was 68%, 50% and 33% in the three mPRS groups (P=0.361) and 71%, 40% and 63%, in the three ELN 2022 categories (P=0.032). In the refractory subcohort, the overall response rate was 69%, 44% and 14% in the mPRS groups (P=0.051) and 100% and 43% in the intermediate and adverse categories when using the ELN 2022 risk stratification (P=0.197). Among patients of the R/R cohort in composite CR with available minimal residual disease data, 18/35 (51%) in the higher-, 6/15 (40%) in the interme-





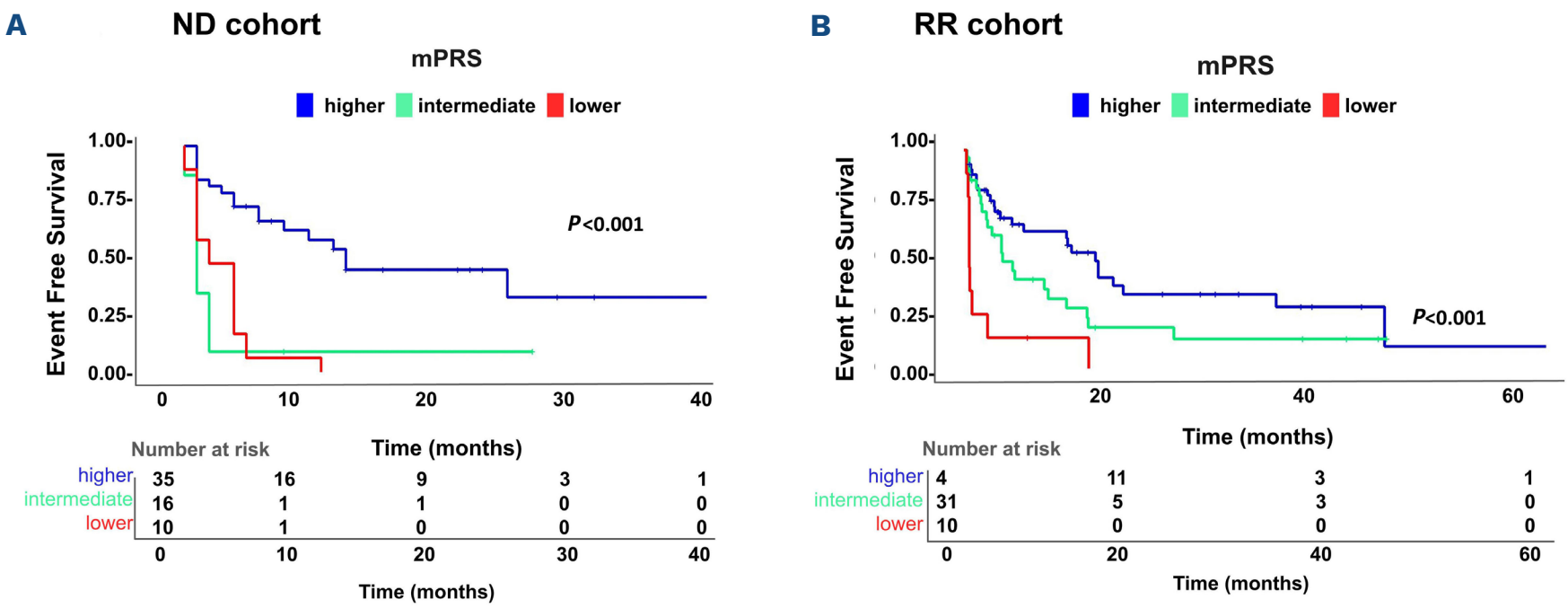


D C-INDEX

	C-INDEX mPRS	C-INDEX ELN 2022	C-INDEX Krüger model	Z-SCORE
ND cohort	0.69	0.59	-	**2.22** (*P*=0.030)
RR cohort	0.61	0.54	0.58	mPRS *vs.* ELN2022 **1.20** (*P*=0.220) Krüger's *vs.* mPRS **-0.81** (*P*=0.410)

	Median OS, months (95% CI)	HR (95% CI)	*P*
mPRS - ND cohort (panel A)			
higher benefit	30.0 (19.0-40.9)		**<0.001**
intermediate benefit	11.0 (3.2-18.8)	2.30 (0.87-6.06)	0.091
lower benefit	4.0 (0.9-7.0)	7.23 (2.83-18.43)	**<0.001**
mPRS - RR cohort (panel B)			
higher benefit	23.6 (0.0-51.9)		**0.015**
intermediate benefit	8.7 (6.7-10.7)	1.81 (0.98-3.34)	0.056
lower benefit	5.6 (2.9-8.4)	3.16 (1.37-7.25)	**0.007**
Krüger model - RR cohort (panel C)			
favorable	37.0 (NA-NA)		0.073
intermediate	13.8 (2.1-25.5)	2.33 (0.56-9.85)	0.246
adverse	9.5 (6.8-12.2)	3.94 (0.92-16.95)	0.066

Figure 1. Overall survival predicted by the molecular prognostic risk signature and Krüger's model in patients with acute myeloid leukemia. (A, B) Overall survival predicted by the molecular prognostic risk signature in patients with newly diagnosed acute myeloid leukemia (A) and in those with relapsed or refractory disease (B). (C) Overall survival according to Krüger's model in the relapsed/refractory cohort. (D) C-index comparisons. ND: newly diagnosed; mPRS: molecular prognostic risk signature; RR: relapsed or refractory; ELN: European LeukemiaNet; OS: overall survival; 95% CI: confidence interval; HR: hazard ratio.



D C-INDEX

	C-INDEX mPRS	C-INDEX ELN 2022	C-INDEX Krüger model	Z-SCORE
ND cohort	0.70	0.49	-	**4.40** (*P*<0.001)
RR cohort	0.63	0.58	0.64	mPRS *vs.* ELN2022 **1.00** (*P*=0.310)

	Median EFS, months (95% CI)	HR (95% CI)	*P*
mPRS - ND cohort (panel A)			
higher benefit	13.0 (0.2-25.7)		**<0.001**
intermediate benefit	1.0 (0.5-1.5)	4.17 (1.98-8.80)	**<0.001**
lower benefit	2.0 (0.0-4.3)	3.93 (1.75-8.89)	**0.001**
mPRS - RR cohort (panel B)			
higher benefit	14.9 (9.4-20.3)		**<0.001**
intermediate benefit	5.7 (3.5-7.9)	1.63 (0.92-2.89)	0.098
lower benefit	1.0 (0.8-1.2)	4.83 (2.20-10.62)	**<0.001**
Krüger model - RR cohort (panel C)			
favorable	14.9 (11.5-NA)		**0.003**
intermediate	5.7 (3.5-13.8)	2.79 (0.66-11.70)	0.162
adverse	1.1 (1.0-NA)	6.09 (1.43-25.93)	**0.015**

Figure 2. Event-free survival predicted by the molecular prognostic risk signature and Krüger's model in patients with acute myeloid leukemia. (A, B) Event-free survival predicted by the molecular prognostic risk signature in patients with newly diagnosed acute myeloid leukemia (A) and in those with relapsed or refractory disease (B). (C) Event-free survival according to Krüger's model in the relapsed/refractory cohort. (D) C-index comparisons. ND: newly diagnosed; mPRS: molecular prognostic risk signature; RR: relapsed or refractory; ELN: European LeukemiaNet; EFS: event-free survival; 95% CI: confidence interval; HR: hazard ratio.

diate- and 2/2 (100%) in the lower-benefit mPRS groups were negative for minimal residual disease (*P*=0.268). The actualization rate of hematopoietic stem cell transplantation differed in the three mPRS categories, with borderline statistical significance (90%, 67% and 63%, respectively; *P*=0.064). The median OS of R/R patients was 24, 9 and 6 months in the higher-, intermediate- and lower-benefit groups according to the mPRS (*P*=0.011; C-index=0.61) (Figure 1B, D); the median EFS was 15, 6 and 1 months, respectively (*P*<0.001; C-index=0.63) (Figure 2B, D). Similar figures for median OS using ELN 2022 categorization were 46, 11 and 11 months for favorable, intermediate and adverse risk categories (*P*=0.091; C-index=0.54) and 46, 9 and 6 months for median EFS, respectively (*P*=0.024; C-index=0.58). The mPRS *versus* ELN 2022 Z-score was 1.20 (*P*=0.220) for OS and 1.00 (*P*=0.310) for EFS. Comparable results were obtained by censoring at the time of hematopoietic stem cell transplantation.

We then evaluated the goodness of fit for outcome prediction of the model independently developed by Krüger *et al*. in our R/R cohort. The mutational frequencies of the genes that are included in Krüger's algorithm in our series are shown in *Online Supplementary Table S1*. According to the model, eight (9%), 51 (57%) and 30 (34%) patients were allocated to the favorable, intermediate and adverse groups, with respective overall response rates of 88%, 71% and 40% (*P*=0.006). The median OS was 37, 14 and 9 months for the favorable, intermediate and adverse categories according to the model (*P*=0.061; C-index 0.58) (Figure 1C, D); the median EFS was 15, 6 and 1 month, respectively (*P*<0.001; C-index 0.64) (Figure 2C, D). This risk stratification model exhibited slightly better performance than the ELN 2022 classification system, but not the mPRS model. In detail, the Z-score for OS was 0.59 for Krüger's model *versus* the ELN 2022 model (*P*=0.550) and -0.81 *versus* the mPRS (*P*=0.410) (Figure 1D).

Finally, we evaluated the performance of the mPRS model in the entire cohort of patients treated with venetoclax-based regimens (*Online Supplementary Figure S1*). The median OS was 30, 9 and 6 months in the higher, intermediate and lower benefit groups according to mPRS (*P*<0.001; C-index=0.64) and 46, 14 and 11 months for favorable, intermediate, and adverse ELN 2022 categories (*P*=0.016; C-index=0.56). The median EFS was 15, 3 and 1 months in the mPRS groups (*P*<0.001; C-index=0.66) and 46, 6 and 6 months in the ELN 2022 categories (*P*=0.013; C-index=0.55). The calculated Z-score for mPRS *versus* ELN 2022 was 2.28 (*P*=0.020) and 3.21 (*P*=0.001) for OS and EFS, respectively, in the entire cohort of venetoclax-treated patients, confirming the better performance of the mPRS model for predicting OS and EFS.

As venetoclax-based regimens are steadily taking the lead in the management of elderly/unfit patients, it soon became apparent that conventional stratification algorithms (e.g., the ELN 2022 risk stratification) have shortcomings in effectively predicting clinical outcomes in such a therapeutic context. In fact, susceptibility and resistance to venetoclax and conventional intensive therapy are believed to originate through different mechanisms. As a consequence, there is an unmet need for stratification model(s) that could provide a reliable tool for clinicians to inform their decisions and to facilitate communication with patients and families. The recently developed mPRS model holds the promise of being able to effectively inform prognosis in ND patients, but whether it is also accurate in R/R settings remains unclear. Furthermore, the purpose of venetoclax-based treatment in the two clinical settings (ND and R/R) often differs, as do the relative populations of patients. The former context generally involves elderly/unfit patients with the primary aim of prolonging survival and the observed inadequacy at estimating initial response does not diminish the utility of mPRS. Conversely, in the R/R setting, venetoclax provides an effective and less toxic bridge to transplant, and the performance of prediction models needs to be measured accordingly. Furthermore, the observed variability in genotypic groups from different models (e.g., mPRS, Krüger) likely reflects the inadequacy of conventional bulk sequencing to capture the dynamics of subclones, their varying dominance, and sensitivity to venetoclax-based therapies.

Overall, our data from a real-world setting confirm the goodness of mPRS in terms of OS and EFS prediction in the ND setting, where it clearly identifies three distinct prognostic groups, and suggest its potential role also for R/R patients, at least for the prediction of the likelihood of response, which is of paramount importance in this subset. The mPRS model might, therefore, be suitably used in clinical practice for all patients receiving venetoclax-based regimens and - together with already validated criteria to assess the fitness[6] - could be used to guide the choice between different therapeutic strategies for AML patients. This notwithstanding, further efforts are warranted to develop and validate new models to predict response to venetoclax-based regimens in larger series, specifically for R/R patients who are treated with the intent of bridging to stem cell transplantation; otherwise, in the case of a predicted unfavorable outcome, these patients might be more suitably addressed to agents in clinical development.

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https://doi.org/10.3324/haematol.2024.285934

Received: June 10, 2024.
Accepted: August 27, 2024.
Early view: September 5, 2024.

Disclosures

AMV, MP, FM and GG received personal fees for advisory board services and/or lectures from AbbVie. The other authors have no conflicts of interest to report.

Contributions

GC, MP and AMV designed research, analyzed and interpreted data, and wrote the manuscript. FM, GG, BB, LF, FC, EQ, AP, JC, GR, FP, LS, CM, FIV and PG contributed data. GC, MP, FM and AMV performed research. All authors participated in interpreting the data. They all checked and approved the final version of the manuscript.

Funding

This work received financial support from Associazione Italiana per la Ricerca sul Cancro (AIRC) 5×1000 called “Metastatic disease: the key unmet need in oncology” to MYNERVA (MYeloid NEoplasms Research Venture AIRC), project #21267. It was also supported by a legacy from the Zottola family to UNIFI.

Data-sharing statement

The aggregated datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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